

# ANALYSIS OF A MATHEMATICAL MODEL FOR THE GROWTH OF CANCER CELLS

MARTIN KOHLMANN

**ABSTRACT.** In this paper, a two-dimensional model for the growth of multi-layer tumors is presented. The model consists of a free boundary problem for the tumor cell membrane and the tumor is supposed to grow or shrink due to cell proliferation or cell dead. The growth process is caused by a diffusing nutrient concentration  $\sigma$  and is controlled by an internal cell pressure  $p$ . We assume that the tumor occupies a strip-like domain with a fixed boundary at  $y = 0$  and a free boundary  $y = \rho(x)$ , where  $\rho$  is a  $2\pi$ -periodic function. First, we prove the existence of solutions  $(\sigma, p, \rho)$  on a scale of small Hölder spaces and show that our model allows for flat stationary solutions. As a main result we establish that these equilibrium points are locally asymptotically stable under small perturbations.

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## 1. INTRODUCTION

The mathematical modeling of cancer growth is a challenging area of research in the applied sciences nowadays. The complex growth process of a tumor cell can be captured within different mathematical models, e.g., models consisting of a system of coupled partial differential equations which arise from reaction-diffusion equations and a mass conservation law [6, 7, 21, 28, 29]. In this context, tumor growth is often considered as a free boundary problem [3, 4, 8–10, 12–15, 30]. Sometimes, it is also justified to treat cancer growth as an incompressible flow in a porous medium so that cells move in accordance with Darcy’s law, see, e.g., [9, 12, 19]. We refer the reader to the review papers [2, 5, 25] which present a variety of other tumor growth models.

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2000 *Mathematics Subject Classification.* 35R35, 35Q92, 35B35.

*Key words and phrases.* Free boundary problem, tumor growth, well-posedness, flat stationary solutions, stability.

Over the years, the following general non-dimensionalized moving boundary value problem

$$(1) \quad \begin{cases} \Delta\sigma = f(\sigma) & \text{in } \Omega(t), \\ \Delta p = -g(\sigma) & \text{in } \Omega(t), \\ \sigma = \bar{\sigma} & \text{on } \partial\Omega(t), \\ p = \gamma\kappa & \text{on } \partial\Omega(t), \\ V = -\partial_\nu p & \text{on } \partial\Omega(t), \end{cases}$$

has turned out to be very appropriate to describe the growth of tumor cells; see, e.g., [19]. Here  $\sigma = \sigma(t, x)$  and  $p = p(t, x)$  are unknown functions defined on the time-space manifold  $\bigcup_{t \geq 0} \{t\} \times \Omega(t)$  with an a priori unknown time-dependent domain  $\Omega(t) \subset \mathbb{R}^n$ . The boundary  $\partial\Omega(t)$  has to be determined together with the functions  $\sigma$  and  $p$  which model the nutrient concentration and the internal pressure for the tumor cell described by  $\Omega(t)$ . Furthermore,  $\bar{\sigma} > 0$  is a constant and  $\kappa$  and  $\partial_\nu$  denote the mean curvature and the normal derivative (with respect to the outward normal) for the boundary  $\partial\Omega$ . Finally,  $\gamma > 0$  is the surface tension coefficient and  $V$  denotes the normal velocity of the free boundary. In (1), the tumor  $\Omega(t)$  receives a constant supply of nutrient on its boundary and the pressure on  $\partial\Omega(t)$  is proportional to the curvature of the free surface  $\partial\Omega(t)$ , as proposed in [22]. The evolution equation for the moving boundary comes from an application of Darcy's law from fluid mechanics. We also impose the initial condition  $\Omega(0) = \Omega_0$ , where  $\Omega_0 \subset \mathbb{R}^n$  is a given bounded domain in  $\mathbb{R}^n$  with a sufficiently smooth boundary.

Typical choices for  $f$  and  $g$  are

$$f(\sigma) = \lambda\sigma, \quad g(\sigma) = \mu(\sigma - \tilde{\sigma})$$

where  $\lambda, \mu, \tilde{\sigma} > 0$  are constants, [6], or

$$\begin{aligned} f(\sigma) &= \beta \frac{A\sigma^{m_1}}{\sigma_c^{m_1} + \sigma^{m_1}} + h(\sigma), \\ g(\sigma) &= \frac{A\sigma^{m_1}}{\sigma_c^{m_1} + \sigma^{m_1}} - B \left( 1 - \frac{\delta\sigma^{m_2}}{\sigma_d^{m_2} + \sigma^{m_2}} \right), \end{aligned}$$

with positive constants  $A, B, \beta, \delta, m_1, m_2, \sigma_c, \sigma_d$  and a non-negative increasing function  $h$ , [28]. In [11], the authors assume that  $f$  and  $g$  are general functions satisfying

- $f, g \in C^\infty[0, \infty)$ ,
- $f'(\sigma) > 0$  for  $\sigma \geq 0$  and  $f(0) = 0$ ,
- $g'(\sigma) > 0$  for  $\sigma \geq 0$  and  $g(\tilde{\sigma}) = 0$  for some  $\tilde{\sigma} > 0$ ,
- $\tilde{\sigma} < \bar{\sigma}$ .

In this paper, we will suppose that

$$f(\sigma) = \sigma, \quad g(\sigma) = \mu(\sigma - \tilde{\sigma}),$$

with positive parameters  $\mu, \tilde{\sigma}$ . Since  $\Delta p$  is minus the divergence of the cell velocity field, the meaning of  $\Delta p = -\mu(\sigma - \tilde{\sigma})$  is that tumor volume is produced, if  $\sigma$  is above the proliferation threshold  $\tilde{\sigma}$ , and that the tumor volume decreases in the opposite case.

The tumor growth model which we study in this paper has the following form: The tumor is assumed to occupy a two-dimensional region of the form

$$\Omega_\rho(t) := \{(x, y) \in \mathbb{R}^2; 0 < y < \rho(t, x)\}$$

where  $t$  is the time variable and  $\rho(t, x)$  is an unknown positive  $2\pi$ -periodic function. The upper boundary of the tumor is denoted as

$$\Gamma_\rho(t) := \{(x, y) \in \mathbb{R}^2; y = \rho(t, x)\},$$

its lower boundary is  $\Gamma_0 = \{(x, y) \in \mathbb{R}^2; y = 0\}$ . A similar situation is discussed in [12] where the authors explain that the strip-shaped model refers to the growth of multi-layer tumors, a kind of in vitro tumors cultivated in laboratory by using the recently developed tissue culture technique, [23, 24, 27]. While there are only a few works dealing with strip-shaped domains, a variety of papers considering radially symmetric models for tumor growth have been published, cf., e.g., the seminal paper [18].

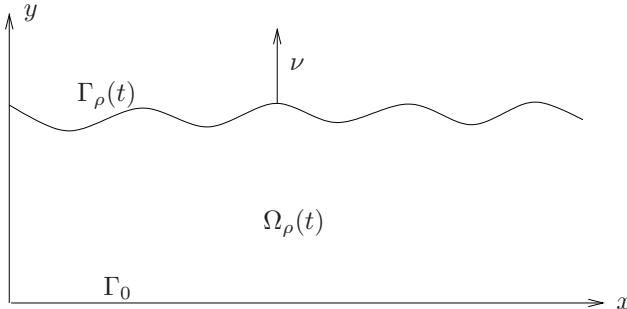


Figure 1: A free boundary problem modeling multi-layer tumors.

The following conditions on the tumor growth process are imposed: We assume that the tumor is constantly supplied with nutrient on  $\partial\Omega_\rho(t)$ ; precisely, the nutrient concentration is  $\bar{\sigma}_2 > 0$  on  $\Gamma_\rho(t)$  and  $\bar{\sigma}_1 > 0$  on  $\Gamma_0$ . As in (1), we assume that the pressure on  $\Gamma_\rho$  is given by  $\gamma\kappa_{\Gamma_\rho}$ . Since tumor cells should only grow in the positive  $y$  direction, we assume that  $p_y = 0$  on  $\Gamma_0$ . Thus we are led to study the following system of equations:

$$(2) \quad \begin{cases} \Delta\sigma = \sigma & \text{in } \Omega_\rho(t), \quad t > 0, \\ \Delta p = -\mu(\sigma - \tilde{\sigma}) & \text{in } \Omega_\rho(t), \quad t > 0, \\ \rho_t = -\frac{\partial p}{\partial \nu} & \text{on } \Gamma_\rho(t), \quad t > 0, \\ \sigma = \bar{\sigma}_2 & \text{on } \Gamma_\rho(t), \quad t > 0, \\ \sigma = \bar{\sigma}_1 & \text{on } \Gamma_0, \quad t > 0, \\ p = \gamma\kappa_{\Gamma_\rho} & \text{on } \Gamma_\rho(t), \quad t > 0, \\ p_y = 0 & \text{on } \Gamma_0, \quad t > 0, \\ \rho = \rho_0 & \text{for } t = 0, \end{cases}$$

where  $\nu = (-\rho_x, 1)$  denotes the outward normal on  $\Gamma_\rho(t)$  with respect to  $\Omega_\rho(t)$  and  $\rho_0$  is a given periodic function. The third equation in (2) can be derived as

follows: we assume that the normal velocity  $V$  of the boundary  $\Gamma_\rho$  is equal to the cell movement velocity in the direction of the outward unit normal

$$\nu_0 = \frac{1}{\sqrt{1 + \rho_x^2}}(-\rho_x, 1),$$

cf. [3, 6, 16, 21, 28]. Then Darcy's law and the relation  $V = \rho_t(1 + \rho_x^2)^{-1/2}$  (cf. [16]) imply that  $V = -\nu_0 \cdot \nabla p$  and that the motion of the free surface  $\Gamma_\rho$  is modeled by the third equation of (2).

In the model presented in [12], the lower boundary  $\Gamma_0$  is supposed to be impermeable for glucose and oxygen. The authors also comment briefly on a variant of their model obtained by exchanging the boundary conditions for  $\sigma$  on  $\Gamma_\rho$  and  $\Gamma_0$ . The novel aspect of the problem presented in the paper at hand is that we allow for supply of nutrient on both boundary components.

Our paper can be outlined as follows: In Section 2, we recall some elementary facts, definitions and notation from [12] which will be important for our approach to the system (2). In Section 3, we prove that the system (2) is well-posed on a scale of small Hölder spaces and we compute its flat stationary solutions. Finally, in Section 4, we linearize the system (2) at such an equilibrium and prove that it is asymptotically stable under small perturbations.

*Acknowledgement.* The author thanks the anonymous referees for helpful suggestions that improved the preliminary version of the paper.

## 2. PRELIMINARIES

Let  $\mathbb{S} = \mathbb{R}/2\pi\mathbb{Z}$ . Function spaces of  $2\pi$ -periodic functions will be identified with the corresponding spaces on  $\mathbb{S}$ . In the following  $C_+([0, T] \times \mathbb{S})$  stands for the cone of all positive functions in  $C([0, T] \times \mathbb{S})$ , for any  $T > 0$ . We will make use of the little Hölder spaces  $h^{k+\alpha}(\mathbb{S})$  which are defined as the closure of  $C^\infty(\mathbb{S})$  in the usual Hölder space  $C^{k+\alpha}(\mathbb{S})$ , for  $k \in \mathbb{N}$  and  $\alpha \in (0, 1)$ . Similarly, for any open set  $\Omega \subset \mathbb{R}^2$ , we define  $h^{k+\alpha}(\overline{\Omega})$  as the closure of  $C^\infty(\overline{\Omega})$  in  $C^{k+\alpha}(\overline{\Omega})$ . The little Hölder spaces are Banach algebras under pointwise multiplication and the embedding  $h^r(\mathbb{S}) \hookrightarrow h^s(\mathbb{S})$ , for  $r > s$ , is compact. We shall denote the cone of positive functions in  $h^{k+\alpha}(\mathbb{S})$  by  $h_+^{k+\alpha}(\mathbb{S})$ .

Let

$$D_{\rho, T} = \{(t, x, y); t \in [0, T], x \in \mathbb{S}, 0 \leq y \leq \rho(t, x)\}.$$

We call a triple  $(\sigma, p, \rho)$  a solution to the problem (2) if

$$\begin{aligned} & (\sigma, p) \in C(D_{\rho, T}) \times C(D_{\rho, T}), \\ & \sigma(t, \cdot) \in h^{4+\alpha}(\overline{\Omega_\rho(t)}), p(t, \cdot) \in h^{2+\alpha}(\overline{\Omega_\rho(t)}), t \in (0, T), \\ & \rho \in C([0, T], h_+^{3+\alpha}(\mathbb{S})) \cap C^1((0, T), h^{1+\alpha}(\mathbb{S})), \\ & (\sigma, p, \rho) \text{ satisfies (2) pointwise on } D_{\rho, T}. \end{aligned}$$

A solution  $(\sigma, p, \rho)$  is called stationary, if  $(\sigma, p, \rho) = (\sigma(x, y), p(x, y), \rho(x))$ . We call a stationary solution flat if  $(\sigma, p) = (\sigma(y), p(y))$  and  $\rho$  is a positive constant. Finally,

we call the problem (2) well-posed if there exist a time  $T > 0$  and a unique solution  $(\sigma, p, \rho)$  on  $[0, T]$  as defined above.

The usual way of treating a free boundary problem like (2) is to transform it to a problem on a fixed reference domain. Let  $\Omega := \mathbb{S} \times (0, 1)$  with the boundary components  $\Gamma_i := \mathbb{S} \times \{i\} \simeq \mathbb{S}$  for  $i \in \{0, 1\}$ . Given any  $\rho \in C_+^2(\mathbb{S})$ , we introduce the map

$$\theta_\rho : \overline{\Omega} \rightarrow \overline{\Omega_\rho}, \quad (x', y') \mapsto (x', y'\rho(x'));$$

i.e., we will label the coordinates in  $\overline{\Omega_\rho}$  by  $(x, y)$  and the variables in  $\overline{\Omega}$  by  $(x', y')$  with the transformation

$$x = x' \quad \text{and} \quad y = y'\rho(x') \quad \text{or} \quad x' = x \quad \text{and} \quad y' = \frac{y}{\rho(x)}.$$

Since  $\rho$  is positive, it follows that  $\theta_\rho$  is a  $C^2$ -diffeomorphism. Let  $u \in C(\overline{\Omega_\rho})$  and  $v \in C(\overline{\Omega})$ . Then

$$\theta_\rho^* u := u \circ \theta_\rho \in C(\overline{\Omega}) \quad \text{and} \quad (\theta_\rho)_* v := v \circ \theta_\rho^{-1} \in C(\overline{\Omega_\rho}).$$

We call  $\theta_\rho^*$  the pull-back and  $(\theta_\rho)_*$  the push-forward operator for the pair  $(\overline{\Omega}, \overline{\Omega_\rho})$ . For  $v \in C^2(\overline{\Omega})$  and  $\rho \in C_+^2(\mathbb{S})$  we define

$$\mathcal{A}(\rho)v := \theta_\rho^* \Delta[(\theta_\rho)_* v], \quad \mathcal{B}(\rho)v := \theta_\rho^* (\text{tr}[\nabla(\theta_\rho)_* v] \cdot \nu),$$

where  $\text{tr}$  denotes the trace operator with respect to  $\Gamma_\rho$ . It is easy to derive the explicit formulae

$$(3) \quad \mathcal{A}(\rho)v = v_{x'x'} - v_{x'y'} \frac{2y'\rho_{x'}}{\rho} + v_{y'y'} \frac{1 + (y')^2 \rho_{x'}^2}{\rho^2} - v_{y'y'} \frac{\rho_{x'x'} \rho - 2\rho_{x'}^2}{\rho^2}$$

and

$$(4) \quad \mathcal{B}(\rho)v = \left( -v_{x'} + v_{y'} \frac{\rho_{x'}}{\rho} \right) \Big|_{y'=1} \rho_{x'} + \frac{1}{\rho} v_{y'} \Big|_{y'=1}.$$

The straightforward calculations leading to (3) and (4) are omitted for the convenience of the reader. We conclude that  $\mathcal{A}$  is uniformly elliptic in  $\overline{\Omega}$ , as defined in [20]. Using the fact that the little Hölder spaces are Banach algebras, it follows that

$$\mathcal{A} \in C^\infty(h_+^{3+\alpha}(\mathbb{S}); \mathcal{L}(h^{2+i+\alpha}(\overline{\Omega}), h^{i+\alpha}(\overline{\Omega}))), \quad i \in \{0, 1\}.$$

and

$$\mathcal{B} \in C^\infty(h_+^{3+\alpha}(\mathbb{S}); \mathcal{L}(h^{2+i+\alpha}(\overline{\Omega}), h^{1+i+\alpha}(\mathbb{S}))), \quad i \in \{0, 1\}.$$

In terms of the variables

$$\tau(t) := \theta_{\rho(t)}^* \sigma(t, \cdot) \quad \text{and} \quad q(t) := \theta_{\rho(t)}^* p(t, \cdot),$$

the system (2) is equivalent to

$$(5) \quad \left\{ \begin{array}{lcl} \mathcal{A}(\rho(t))\tau & = & \tau & \text{in } \Omega, & t > 0, \\ \mathcal{A}(\rho(t))q & = & -\mu(\tau - \tilde{\sigma}) & \text{in } \Omega, & t > 0, \\ \rho_t & = & -\mathcal{B}(\rho(t))q & \text{on } \Gamma_1, & t > 0, \\ \tau & = & \bar{\sigma}_2 & \text{on } \Gamma_1, & t > 0, \\ \tau & = & \bar{\sigma}_1 & \text{on } \Gamma_0, & t > 0, \\ q & = & \gamma\kappa & \text{on } \Gamma_1, & t > 0, \\ q_y & = & 0 & \text{on } \Gamma_0, & t > 0, \\ \rho & = & \rho_0 & & \text{for } t = 0. \end{array} \right.$$

Next, we introduce the following solution operators: The solution of the boundary value problem

$$\left\{ \begin{array}{lcl} \mathcal{A}(\rho)\tau & = & \tau & \text{in } \Omega, \\ \tau & = & \bar{\sigma}_1 & \text{on } \Gamma_0, \\ \tau & = & \bar{\sigma}_2 & \text{on } \Gamma_1 \end{array} \right.$$

is denoted as  $\tau = \mathcal{R}(\rho)(\bar{\sigma}_1, \bar{\sigma}_2)$ . For given functions  $f \in h^{1+\alpha}(\overline{\Omega})$  and  $k \in h^{2+\alpha}(\mathbb{S})$ , we write the solution of

$$\left\{ \begin{array}{lcl} \mathcal{A}(\rho)q & = & f & \text{in } \Omega, \\ q_y & = & 0 & \text{on } \Gamma_0, \\ q & = & k & \text{on } \Gamma_1 \end{array} \right.$$

as  $q = \mathcal{S}(\rho)f + \mathcal{T}(\rho)k$ . We have

$$\mathcal{R}(\cdot)(\bar{\sigma}_1, \bar{\sigma}_2) \in C^\infty(h_+^{3+i+\alpha}(\mathbb{S}); h^{3+i+\alpha}(\overline{\Omega})), \quad i \in \{0, 1\},$$

and

$$(\mathcal{S}, \mathcal{T}) \in C^\infty(h_+^{3+\alpha}(\mathbb{S}); \mathcal{L}(h^{1+\alpha}(\overline{\Omega}), h^{3+\alpha}(\overline{\Omega})) \times \mathcal{L}(h^{2+\alpha}(\mathbb{S}), h^{2+\alpha}(\overline{\Omega}))).$$

Since the sign of  $\kappa$  determines the following results in a very significant way, it will be very instructive to remind the reader of the following elementary result: In classical differential geometry one considers a local parametrization  $c(x) = (x, \rho(x))$  of the curve  $\Gamma_\rho$  and has

$$\kappa(x) = \frac{|c_x(x) \times c_{xx}(x)|}{|c_x(x)|^3} = (1 + \rho_x^2)^{-3/2} \rho_{xx}.$$

Note however that the boundary  $\Gamma_\rho$  is convex in  $(x, \rho(t, x))$  with respect to the outer normal of  $\Omega_\rho$  if and only if  $\rho(t, x)$  is concave in  $x$  and vice versa. This motivates to change the sign of the classical curvature formula so that we will use the identity

$$\kappa = -(1 + \rho_x^2)^{-3/2} \rho_{xx}$$

for the curvature of  $\Gamma_\rho$ . With this modified sign convention we write

$$\kappa_{\Gamma_\rho} = \mathcal{P}(\rho)\rho,$$

where

$$\mathcal{P}(\rho) = -(1 + \rho_x^2)^{-3/2} \partial_x^2 \in C^\infty(h_+^{3+\alpha}(\mathbb{S}); \mathcal{L}(h^{4+\alpha}(\mathbb{S}), h^{2+\alpha}(\mathbb{S}))).$$

### 3. WELL-POSEDNESS AND THE FLAT STATIONARY SOLUTIONS

In this section, we discuss the question of existence and uniqueness of a solution to (2). In particular, we are interested in stationary solutions to (2), i.e., solutions which do not depend on time. We begin with a proof of the following theorem. In fact, the arguments are just a repetition of what is derived in [12].

**Theorem 1.** *Given  $\rho_0 \in h_+^{3+\alpha}(\mathbb{S})$ , there exists  $T > 0$  such that (2) has a solution which is unique in the class  $C(D_{\rho,T}) \times C(D_{\rho,T}) \times C([0, T], h_+^{3+\alpha}(\mathbb{S}))$ . Furthermore, if  $\rho_0 \in h_+^{4+\alpha}(\mathbb{S})$ , then  $\rho \in C([0, T], h_+^{4+\alpha}(\mathbb{S})) \cap C^1([0, T], h^{1+\alpha}(\mathbb{S}))$ .*

*Proof.* Using the notation of Section 2, it is easy to see that the transformed system (5) can be written in the form

$$(6) \quad \begin{cases} \rho_t + \Phi(\rho)\rho = F(\rho), & t > 0, \\ \rho = \rho_0, & t = 0, \end{cases}$$

where

$$\Phi(\rho) = \gamma \mathcal{B}(\rho) \mathcal{T}(\rho) \mathcal{P}(\rho) \quad \text{and} \quad F(\rho) = \mu \mathcal{B}(\rho) \mathcal{S}(\rho) \{\mathcal{R}(\rho)(\bar{\sigma}_1, \bar{\sigma}_2) - \tilde{\sigma}\}.$$

We find that

$$(7) \quad (\Phi, F) \in C^\infty(h_+^{3+\alpha}(\mathbb{S}); \mathcal{L}(h_+^{4+\alpha}(\mathbb{S}), h_+^{1+\alpha}(\mathbb{S})) \times h_+^{2+\alpha}(\mathbb{S})).$$

Since  $\gamma > 0$ , the operator  $\Phi(\rho)$  generates, for any  $\rho \in h_+^{3+\alpha}(\mathbb{S})$ , a strongly continuous analytic semigroup on the space  $h_+^{1+\alpha}(\mathbb{S})$  (cf. Theorem 4.1. in [17]). An application of Amann's local existence, uniqueness and regularity theory for abstract quasilinear evolution equations (see, e.g., Theorem 12.1 and Remarks 12.2 in [1]) achieves the proof.  $\square$

To find the flat stationary solutions  $(\sigma_*(y), p_*(y), \rho_*)$  of (2) we first solve the problem

$$\begin{cases} \sigma_*'' = \sigma_*, \\ \sigma_*(0) = \bar{\sigma}_1, \\ \sigma_*(\rho_*) = \bar{\sigma}_2, \end{cases}$$

and obtain the unique solution

$$(8) \quad \sigma_*(y) = (\bar{\sigma}_2 - \bar{\sigma}_1 \cosh \rho_*) \frac{\sinh y}{\sinh \rho_*} + \bar{\sigma}_1 \cosh y.$$

Next, we observe that the unique solution of

$$\begin{cases} p_*'' = -\mu(\sigma_* - \tilde{\sigma}), \\ p_*(\rho_*) = 0, \\ p'_*(0) = 0 \end{cases}$$

is given by

$$(9) \quad p_*(y) = \mu \frac{\bar{\sigma}_2 - \bar{\sigma}_1 \cosh \rho_*}{\sinh \rho_*} (y - \rho_*) + \mu \left( \bar{\sigma}_2 - \sigma_*(y) - \frac{1}{2} \tilde{\sigma}(\rho_*^2 - y^2) \right).$$

Since we must demand  $p'(\rho_*) = 0$ , we get the condition

$$(10) \quad \frac{\bar{\sigma}_1 + \bar{\sigma}_2}{\tilde{\sigma}} (1 - \cosh \rho_*) + \rho_* \sinh \rho_* = 0.$$

Let  $\alpha = \frac{\bar{\sigma}_1 + \bar{\sigma}_2}{\tilde{\sigma}}$ . We suppose

$$(11) \quad \bar{\sigma}_1, \bar{\sigma}_2 > \tilde{\sigma}$$

to obtain that  $\alpha > 2$ . The function

$$f_\alpha : (0, \infty) \rightarrow \mathbb{R}, \quad x \mapsto \alpha(1 - \cosh x) + x \sinh x$$

clearly satisfies

$$\lim_{x \rightarrow 0} f_\alpha(x) = 0, \quad \lim_{x \rightarrow \infty} f_\alpha(x) = \infty, \quad f'_\alpha(x) = \cosh x(x + (1 - \alpha) \tanh x).$$

By (11), we conclude that there is a unique  $\rho_* > 0$  with  $f_\alpha(\rho_*) = 0$ . Now the triple  $(\sigma_*, p_*, \rho_*)$  constitutes the unique flat stationary solution of (2).

The condition (11) is also reasonable concerning the long-time behavior of our model: Let

$$\text{Vol}(\Omega_\rho(t)) = \int_0^1 \rho(t, x) dx$$

denote the tumor volume. Using the condition  $p_y(x, 0) = 0$  and the periodic boundary conditions for  $p_x$ , an application of the Gauss-Green Theorem shows that

$$\frac{d}{dt} \text{Vol}(\Omega_\rho(t)) = \int_0^1 \rho_t(t, x) dx = - \int_{\partial\Omega_\rho(t)} \frac{\partial p}{\partial \nu} dx = - \int_{\Omega_\rho(t)} \Delta p d(x, y).$$

Applying the maximum principle, we conclude that

$$(12) \quad \frac{d}{dt} \text{Vol}(\Omega_\rho(t)) = \mu \int_{\Omega_\rho(t)} (\sigma - \tilde{\sigma}) d(x, y) \leq \mu(\max\{\bar{\sigma}_1, \bar{\sigma}_2\} - \tilde{\sigma}) \text{Vol}(\Omega_\rho(t)).$$

Now (11) guarantees that the right-hand side of (12) is positive; otherwise we would have  $\text{Vol}(\Omega_\rho(t)) \rightarrow 0$ , as  $t \rightarrow \infty$ , meaning that the tumor will eventually vanish.

We have proved the following theorem.

**Theorem 2.** *Assume that the condition (11) is satisfied. Then the problem (2) has a unique flat stationary solution  $(\sigma_*, p_*, \rho_*)$  which is determined by the formulas (8), (9) and (10).*

#### 4. THE LINEARIZATION AND ASYMPTOTIC STABILITY

After studying local solvability and regularity of fully nonlinear equations, the second step is to consider the asymptotic behavior and in particular stability of the stationary solutions. Recall that a stationary solution  $\bar{u}$  of an autonomous problem  $u'(t) = F(u(t))$ ,  $t > 0$ , is called stable if for each  $\varepsilon > 0$  there is  $\delta > 0$  such that for  $\|u_0 - \bar{u}\| < \delta$ , we have that  $\|u(t) - \bar{u}\| < \varepsilon$  for any  $t > 0$ , and the solution  $u = u(t; u_0)$  exists for all  $t > 0$  (denoted as  $\tau(u_0) = \infty$ ). The stationary solution  $\bar{u}$  is called asymptotically stable if it is stable and in addition  $\|u(t) - \bar{u}\| \rightarrow 0$  as  $t \rightarrow \infty$ , uniformly for  $u_0$  in a neighborhood of  $\bar{u}$ . It is said to be unstable if it is not stable, [26].

In this section, it is our aim to prove that the stationary point  $(\sigma_*, p_*, \rho_*)$  obtained in the previous section is asymptotically stable. Therefore, we consider the

linearization of (5): we plug the ansatz

$$\begin{pmatrix} \tau \\ q \\ \rho \end{pmatrix} = \begin{pmatrix} \sigma_*(y'\rho_*) \\ p_*(y'\rho_*) \\ \rho_* \end{pmatrix} + \varepsilon \begin{pmatrix} \Sigma(t, x', y') \\ P(t, x', y') \\ r(t, x') \end{pmatrix}$$

for  $\varepsilon > 0$  small and with the new unknowns  $(\Sigma, P, r)$  into (5) and compute the derivative with respect to  $\varepsilon$  at  $\varepsilon = 0$ . This yields

$$(13) \quad \left\{ \begin{array}{lcl} \Sigma_{x'x'} + \frac{1}{\rho_*^2} \Sigma_{y'y'} & = & b(\sigma_*)r + \Sigma \quad \text{in } \Omega \times (0, T), \\ P_{x'x'} + \frac{1}{\rho_*^2} P_{y'y'} & = & b(p_*)r - \mu\Sigma \quad \text{in } \Omega \times (0, T), \\ r_t + \frac{1}{\rho_*} P_{y'}|_{y'=1} & = & 0 \quad \text{on } \mathbb{S} \times (0, T), \\ \Sigma|_{y'=1} & = & 0 \quad \text{on } \mathbb{S} \times (0, T), \\ P|_{y'=1} & = & -\gamma r_{x'x'} \quad \text{on } \mathbb{S} \times (0, T), \\ \Sigma|_{y'=0} & = & 0 \quad \text{on } \mathbb{S} \times (0, T), \\ P_{y'}|_{y'=0} & = & 0 \quad \text{on } \mathbb{S} \times (0, T), \\ r & = & r_0, \quad t = 0, \end{array} \right.$$

where

$$b(v)r = \frac{2r}{\rho_*}v''(y'\rho_*) + r_{x'x'}y'v'(y'\rho_*), \quad v \in C^2[0, 1].$$

For a given function  $r \in h^{4+\alpha}(\mathbb{S})$ , we solve the boundary value problem for  $\Sigma$  in (13) and obtain a unique solution  $\Sigma \in h^{4+\alpha}(\overline{\Omega})$ , which is periodic in  $x$ . Substituting  $\Sigma$  into the second line we get a linear problem for  $P$ . Solving the equation for  $P$  with the corresponding boundary conditions, we obtain a function  $P \in h^{2+\alpha}(\overline{\Omega})$  which is also periodic in  $x$ ; observe that  $\gamma r_{x'x'} \in h^{2+\alpha}(\mathbb{S})$ . Let us now introduce an operator  $A \in \mathcal{L}(h^{4+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$  by setting

$$(14) \quad (Ar)(x') = \frac{1}{\rho_*} \frac{\partial P}{\partial y'}(x', 1), \quad x' \in \mathbb{S}.$$

Let

$$\Psi(\rho) := \Phi(\rho)\rho - F(\rho), \quad \rho \in h^{4+\alpha}(\mathbb{S}).$$

By (7), we have  $\Psi \in C^\infty(h_+^{4+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$  and (6) shows that  $\rho_t = -\Psi(\rho)$  for any solution  $\rho$  of (2). With

$$-D\Psi(\rho_*)r = -\left. \frac{d}{d\varepsilon} \Psi(\rho_* + \varepsilon r) \right|_{\varepsilon=0} = \left. \frac{d}{d\varepsilon} (\rho_* + \varepsilon r)_t \right|_{\varepsilon=0} = r_t$$

and the third equation in (13) we see that  $A = D\Psi(\rho_*)$ .

As in [12], we can conclude the following proposition.

**Proposition 3.** *We have  $A \in \mathcal{L}(h^{4+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$ , and  $-A$ , considered as an unbounded operator in  $h^{1+\alpha}(\mathbb{S})$ , generates a strongly continuous analytic semigroup.*

It is our goal to represent the operator  $A$  introduced in (14) as a Fourier multiplication operator. To do so, we use that the functions  $r \in h^{4+\alpha}(\mathbb{S})$ ,  $\Sigma \in h^{4+\alpha}(\overline{\Omega})$  and  $P \in h^{2+\alpha}(\overline{\Omega})$  are periodic with respect to the variable  $x'$ . We thus have the

expansions

$$\begin{pmatrix} r(x') \\ \Sigma(x', y') \\ P(x', y') \end{pmatrix} = \begin{pmatrix} a_0 \\ A_0(y') \\ M_0(y') \end{pmatrix} + \sum_{k=1}^{\infty} \begin{pmatrix} a_k & b_k \\ A_k(y') & B_k(y') \\ M_k(y') & N_k(y') \end{pmatrix} \cdot \begin{pmatrix} \cos(kx') \\ \sin(kx') \end{pmatrix}.$$

**Proposition 4.** *The operator  $A$  is a Fourier multiplication operator, i.e., given  $r \in C^\infty(\mathbb{S})$  with the Fourier expansion*

$$r(x') = a_0 + \sum_{k=1}^{\infty} (a_k \cos(kx') + b_k \sin(kx')),$$

the image  $Ar$  has the Fourier expansion

$$(Ar)(x') = \lambda_0 a_0 + \sum_{k=1}^{\infty} \lambda_k (a_k \cos(kx') + b_k \sin(kx'))$$

with

$$\begin{aligned} \lambda_k &= \frac{\mu(\bar{\sigma}_2 \cosh \rho_* - \bar{\sigma}_1) \sqrt{1+k^2}}{\sinh \rho_* \sinh(\rho_* \sqrt{1+k^2}) \cosh(\rho_* k)} \left( \cosh(\rho_* \sqrt{1+k^2}) \cosh(\rho_* k) - 1 \right) \\ (15) \quad &+ \left( \gamma k^2 - \mu \tilde{\sigma} \rho_* - \mu \frac{\bar{\sigma}_2 - \bar{\sigma}_1 \cosh \rho_*}{\sinh \rho_*} \right) k \tanh(\rho_* k) + \mu(\tilde{\sigma} - \bar{\sigma}_2). \end{aligned}$$

Moreover, the spectrum  $\sigma(A)$  of  $A$  is

$$\sigma(A) = \{\lambda_k; k \in \mathbb{N}_0\}$$

and  $\sigma(A) \subset \mathbb{R}_+$  for sufficiently large  $\gamma$ .

*Proof.* To simplify notation, we will write

$$c_1 = \frac{\bar{\sigma}_2 - \bar{\sigma}_1 \cosh \rho_*}{\sinh \rho_*}, \quad c_2 = \bar{\sigma}_1, \quad c_3 = c_1 \cosh \rho_* + c_2 \sinh \rho_*$$

in the sequel. First, we solve the boundary value problems

$$\begin{cases} -k^2 A_k(y') + \frac{1}{\rho_*^2} A_k''(y') &= A_k(y') + a_k f_k(y'), \\ A_k(0) &= 0, \\ A_k(1) &= 0, \end{cases}$$

for  $k \in \mathbb{N}_0$ , and

$$\begin{cases} -k^2 B_k(y') + \frac{1}{\rho_*^2} B_k''(y') &= B_k(y') + b_k f_k(y'), \\ B_k(0) &= 0, \\ B_k(1) &= 0, \end{cases}$$

for  $k \in \mathbb{N}$ , with

$$f_k(y') = \frac{2}{\rho_*} (c_1 \sinh(y' \rho_*) + c_2 \cosh(y' \rho_*)) - k^2 y' (c_1 \cosh(y' \rho_*) + c_2 \sinh(y' \rho_*)).$$

A lengthy and somewhat tedious computation shows that

$$\begin{aligned} A_k(y') &= a_k c_1 \left( y' \cosh(y' \rho_*) - \frac{\sinh(y' \rho_* \sqrt{1+k^2})}{\sinh(\rho_* \sqrt{1+k^2})} \cosh \rho_* \right) \\ &\quad + a_k c_2 \left( y' \sinh(y' \rho_*) - \frac{\sinh(y' \rho_* \sqrt{1+k^2})}{\sinh(\rho_* \sqrt{1+k^2})} \sinh \rho_* \right), \end{aligned}$$

and  $B_k(y')$  is obtained from  $A_k(y')$  by exchanging  $a_k$  with  $b_k$ . The next task is to solve the boundary value problems

$$\begin{cases} -k^2 M_k(y') + \frac{1}{\rho_*^2} M_k''(y') &= -\mu A_k(y') + a_k g_k(y'), \\ M_k'(0) &= 0, \\ M_k(1) &= \gamma k^2 a_k, \end{cases}$$

for  $k \in \mathbb{N}_0$ , and

$$\begin{cases} -k^2 N_k(y') + \frac{1}{\rho_*^2} N_k''(y') &= -\mu B_k(y') + b_k g_k(y'), \\ N_k'(0) &= 0, \\ N_k(1) &= \gamma k^2 b_k, \end{cases}$$

for  $k \in \mathbb{N}$ , with

$$\begin{aligned} g_k(y') &= \frac{2}{\rho_*} \mu (\tilde{\sigma} - c_1 \sinh(y' \rho_*) - c_2 \cosh(y' \rho_*)) \\ &\quad - k^2 \mu (c_1 y' + \tilde{\sigma} \rho_* (y')^2 - c_2 y' \sinh(y' \rho_*) - c_1 y' \cosh(y' \rho_*)). \end{aligned}$$

Again, it is straightforward to derive the solutions

$$\begin{aligned} M_0(y') &= -\frac{a_0 \mu c_3}{\sinh \rho_*} (y' \rho_* - \rho_* - \sinh(y' \rho_*)) - a_0 \mu \tilde{\sigma} \rho_* - a_0 \mu c_1 \\ &\quad + a_0 \mu c_1 y' + a_0 \mu \tilde{\sigma} \rho_* (y')^2 - a_0 \mu (c_1 y' \cosh(y' \rho_*) + c_2 y' \sinh(y' \rho_*)) \end{aligned}$$

and, for  $k \neq 0$ ,

$$\begin{aligned} M_k(y') &= -\frac{a_k \mu c_3 \sqrt{1+k^2}}{k \sinh(\rho_* \sqrt{1+k^2})} (\sinh(y' \rho_* k) - \tanh(\rho_* k) \cosh(y' \rho_* k)) \\ &\quad + a_k \mu c_3 \frac{\sinh(y' \rho_* \sqrt{1+k^2})}{\sinh(\rho_* \sqrt{1+k^2})} + a_k (\gamma k^2 - \mu \tilde{\sigma} \rho_* - \mu c_1) \frac{\cosh(y' \rho_* k)}{\cosh(\rho_* k)} \\ &\quad + a_k \mu c_1 y' + a_k \mu \tilde{\sigma} \rho_* (y')^2 - a_k \mu (c_1 y' \cosh(y' \rho_*) + c_2 y' \sinh(y' \rho_*)); \end{aligned}$$

the  $N_k$  are obtained from  $M_k$  by replacing  $a_k$  with  $b_k$ . By the definition of  $A$ , we see that  $A$  is a Fourier multiplication operator with

$$\lambda_k = \frac{1}{a_k \rho_*} M'_k(1).$$

Since  $h^{4+\alpha}(\mathbb{S})$  is compactly embedded into  $h^{1+\alpha}(\mathbb{S})$  and the resolvent set  $\rho(A)$  is non-empty, the resolvent operator  $(A - \lambda)^{-1}$  is compact for any  $\lambda \notin \sigma(A)$ . Hence the spectrum  $\sigma(A)$  of  $A$  consists entirely of eigenvalues. Our explicit computations

show that, for all  $k \in \mathbb{N}_0$ ,

$$\begin{aligned}\lambda_k = & -\frac{\mu c_3 \sqrt{1+k^2}}{\sinh(\rho_* \sqrt{1+k^2}) \cosh(\rho_* k)} + \frac{\mu c_3 \sqrt{1+k^2}}{\tanh(\rho_* \sqrt{1+k^2})} \\ & + (\gamma k^2 - \mu \tilde{\sigma} \rho_* - \mu c_1) k \tanh(\rho_* k) \\ & + 2\mu \tilde{\sigma} + \frac{\mu}{\rho_*} (c_1 - c_3) - \mu (c_1 \sinh \rho_* + c_2 \cosh \rho_*),\end{aligned}$$

and, by our definitions,  $\lambda_k$  is as specified in (15). Concerning positivity, we first concentrate our attention on  $\lambda_0$ . Using once again Eq. (10), we obtain

$$\lambda_0 = \mu \tilde{\sigma} \left( 1 - \frac{\rho_*}{\sinh \rho_*} \right),$$

and written in this form,  $\lambda_0$  is clearly positive. For  $k \neq 0$ , fix some  $\gamma_0 > 0$  and let  $\lambda_k(\gamma_0)$  be as in (15). Since

$$\frac{\lambda_k(\gamma_0)}{k^3 \tanh(\rho_* k)} = \gamma_0 + n_k, \quad n_k \rightarrow 0 \text{ for } k \rightarrow \infty,$$

we see that there exists  $k_0 \in \mathbb{N}$  such that  $\lambda_k(\gamma_0) > 0$  for all  $k > k_0$ . Since  $\lambda_k(\gamma) \geq \lambda_k(\gamma_0)$  for  $\gamma \geq \gamma_0$ , it follows that  $\lambda_k(\gamma) > 0$  for all  $k > k_0$  and  $\gamma \geq \gamma_0$ . It is obvious that we can choose  $\gamma \geq \gamma_0$  so large that also  $\lambda_1(\gamma), \dots, \lambda_{k_0}(\gamma) > 0$ . Let  $\Lambda \neq \emptyset$  be the collection of all  $\gamma > 0$  such that  $\lambda_k(\gamma) > 0$  for all  $k \in \mathbb{N}$ . We have shown that  $\sigma(A) \subset \mathbb{R}_+$  for any  $\gamma \in \Lambda$  and this achieves the proof.  $\square$

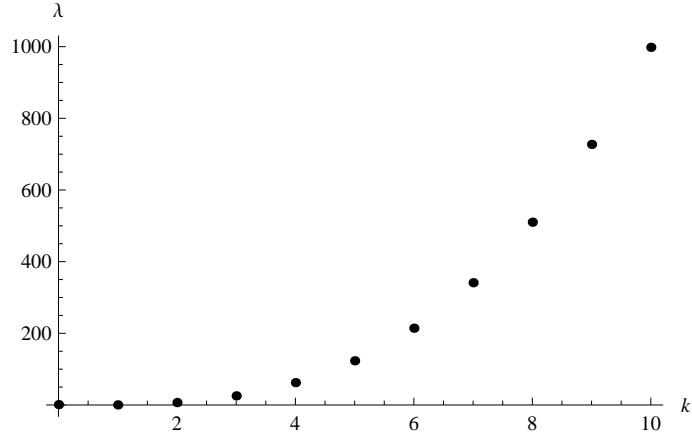


Figure 2: The spectrum of the operator  $A$ , for  $\mu = \tilde{\sigma} = \gamma = 1$ ,  $\bar{\sigma}_1 = 2$ ,  $\bar{\sigma}_2 = 3$ .

In fact, not the operator  $A$  but  $-A$  will determine the stability properties of the problem (2). We will employ the following stability theorem.

**Theorem 5** (see [26]). *Let  $X$  be a Banach space and let  $T: D(T) \subset X \rightarrow X$  be a linear sectorial operator such that the graph norm of  $T$  is equivalent to the norm of  $D$ . Assume furthermore that*

$$\sup\{\operatorname{Re} \lambda, \lambda \in \sigma(T)\} = -\omega_0 < 0.$$

Let  $\mathcal{O}$  be a neighborhood of zero in  $D$  and let  $G: \mathcal{O} \rightarrow X$  be a  $C^1$  function with locally Lipschitz continuous derivative such that  $G(0) = 0$  and  $G'(0) = 0$ . Fix  $\omega \in [0, \omega_0)$ . Then there exist  $r > 0$  and  $M > 0$  such that for each  $u_0 \in B(0, r) \subset D$  the solution  $u(t)$  to the problem

$$u'(t) = Tu(t) + G(u(t)), \quad t > 0, \quad u(0) = u_0,$$

satisfies  $\tau(u_0) = \infty$  and

$$\|u(t)\|_D + \|u'(t)\|_X \leq M e^{-\omega t} \|u_0\|_D, \quad t \geq 0.$$

As for the model in [12], we show that the steady state  $\rho_*$  of

$$(16) \quad \rho_t + \Psi(\rho) = 0, \quad \rho(0) = \rho_0,$$

is asymptotically stable under small perturbations belonging to  $h_+^{4+\alpha}(\mathbb{S})$ . By definition,  $\Psi(\rho) = \Phi(\rho)\rho - F(\rho)$ , for  $\rho \in h_+^{4+\alpha}(\mathbb{S})$ . Setting  $G(r) := \Psi(r + \rho_*) - Ar$ , we have that

$$G \in C^\infty(h_+^{4+\alpha}(\mathbb{S}), h^{1+\alpha}(\mathbb{S}))$$

and observe that

$$G(0) = \Psi(\rho_*) = 0, \quad DG(0) = D\Psi(\rho_*) - A = 0.$$

Theorem 5 implies that the solution  $r$  to

$$r_t = -Ar - G(r)$$

is asymptotically stable: There are constants  $\omega, \varepsilon, K$  such that if  $r_0 \in h_+^{4+\alpha}(\mathbb{S})$  satisfies  $\|r_0\|_{C^{4+\alpha}} < \varepsilon$  then the solution  $r$  exists globally and satisfies

$$\|r(t)\|_{C^{4+\alpha}} \leq K \exp(-\omega t) \|r_0\|_{C^{4+\alpha}}, \quad t \geq 0.$$

Letting  $r(t) = \rho(t) - \rho_*$  for  $t \geq 0$ , this in turn shows that if  $\|\rho_0 - \rho_*\|_{C^{4+\alpha}} < \varepsilon$ , then the solution to (16) exists globally and satisfies

$$(17) \quad \|\rho(t) - \rho_*\|_{C^{4+\alpha}} \leq K \exp(-\omega t) \|\rho_0 - \rho_*\|_{C^{4+\alpha}}, \quad t \geq 0.$$

Next let us consider the dynamical behavior of  $\sigma$  and  $p$ . By definition, we have

$$\sigma_* = \mathcal{R}(\rho_*)(\bar{\sigma}_1, \bar{\sigma}_2) \quad \text{and} \quad \sigma(t) = \mathcal{R}(\rho(t))(\bar{\sigma}_1, \bar{\sigma}_2).$$

By the mean value theorem, there exists a constant  $C$  such that

$$\|\sigma(t) - \sigma_*\|_{C^{4+\alpha}} = \|[\mathcal{R}(\rho(t)) - \mathcal{R}(\rho_*)](\bar{\sigma}_1, \bar{\sigma}_2)\|_{C^{4+\alpha}} \leq C \|\rho(t) - \rho_*\|_{C^{4+\alpha}}$$

for any  $t \geq 0$ . Combining this with estimate (17), we get

$$\|\sigma(t) - \sigma_*\|_{C^{4+\alpha}} \leq K \exp(-\omega t).$$

A corresponding estimate for  $p$  can be obtained similarly. We have proved the following theorem.

**Theorem 6.** *Let  $\bar{\sigma}_1, \bar{\sigma}_2 > \tilde{\sigma} > 0$ ,  $\mu > 0$  and  $\gamma \in \Lambda$  be given. Then the flat stationary solution defined by (8), (9) and (10) is asymptotically stable: There are positive constants  $\omega, K$  and  $\varepsilon$  such that if  $\|\rho_0 - \rho_*\|_{C^{4+\alpha}} < \varepsilon$  then*

$$\|\sigma(t) - \sigma_*\|_{C^{4+\alpha}} + \|p(t) - p_*\|_{C^{2+\alpha}} + \|\rho(t) - \rho_*\|_{C^{4+\alpha}} \leq K \exp(-\omega t),$$

for any  $t \geq 0$ .

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PETER L. REICHERTZ INSTITUTE FOR MEDICAL INFORMATICS, UNIVERSITY OF BRAUNSCHWEIG,  
D-38106 BRAUNSCHWEIG, GERMANY  
*E-mail address:* martin.kohlmann@plri.de